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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,555	09/17/2001	Richard R. Bott	GC278-C3	1655

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/955,555	BOTT ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-29 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-16 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that a search and examination of the entire application (or Groups I and II) can be made without serious burden to the examiner. Applicants argument is not found persuasive because while the searches for the each of the groups overlap, they are not coextensive. For example, search of Group II would require search of subclass 435/69.1, a search of which would be unnecessary the search of the elected group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10.

Priority

Applicants amendment of the first line of the specification to state that this application is a continuation of Serial No. 08/559,968, filed November 17, 1995-- is acknowledged. It is further noted that application No. 08/559,968 claims the benefit of 60/005,701, filed 10/17/1995. It is pointed out to applicants that prior to the above

amendment of the first line of the specification, the first line of the specification recited "This application claims the benefit of U.S. Provisional Application No. _____(Our Docket No. GC278) filed October 17, 1995", and this statement has not been amended or completed with the above entry.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 7, filed 10/15/2002, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

Figures 1, 4 and 6 contain amino acid and/or nucleic acid sequences and are thus subject to the sequence rules. See MPEP, 2422.02, The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures:

> .... when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "heterologous" in claim 1 (claims 2-16 dependent from) is used by the claim to mean "two or more proteins or enzymes which are derived from taxonomically distinct organisms," while the accepted meaning is " two or more proteins or enzymes which are not normally associated with each other". For the sake of advancing prosecution the phrase is interpreted as " two or more proteins or enzymes which are not normally associated with each other".

Claim 7 is indefinite in the recitation of "a dockerin derived from Clostridium sp. or a derivative thereof capable of non-covalently binding to said peptide backbone" as the specification fails to teach which identifying characteristics distinguish a "a derivative of a dockerin derived from *Clostridium* sp." from "dockerins" derived from other species. The application teaches that a "dockerin" means a peptide sequence which is capable of attaching in a non-covalent manner to a peptide backbone and is derived from *C.*

thermocellum but does not define the structural relationship of a dockerin derived from *C. thermocellum* to a *C. thermocellum* dockerin, or how this relates to a dockerin derived from other species.

Claim 13 recites the limitation "...said internal repeating units". There is insufficient antecedent basis for "said internal repeating units" in claim 12, from which this claim depends. Claim 11, from which claim 12 depends recites "...internal repeating elements" and for the sake of advancing prosecution the claim is interpreted as "said internal repeating units" means "said internal repeating elements". It is suggested that applicants maintain consistency throughout the application.

Claim 16 recites the limitation "...said peptide backbone with said enzymatic activity...". There is insufficient antecedent basis for "said enzymatic activity" in the claim.

Further claim 16 is indefinite in that it is confusing and unclear in how "an enzymatic activity" is combined with a peptide backbone. For the purpose of compact prosecution this claim is interpreted as meaning "said peptide backbone with said enzyme".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 are directed to a genus of compositions comprising one or more enzymes non-covalently bound to a peptide backbone, wherein at least one of said enzymes is heterologous to said peptide backbone and said peptide backbone is capable of having bound thereto a plurality of enzymes (claims 1-3, 6 and 7), wherein said peptide backbone comprises scaffoldin derived from a microorganism which produces a cellulosomal or amylosomal complex (claim 4, 5 and 11-13). Claims 14-16 are directed to a genus of compositions comprising any scaffoldin protein or any peptide backbone bound to any enzyme or any array of enzymes wherein said composition is produced recombinantly.

The specification, however, only provides the representative species of these claims encompassed by a composition comprising one or more enzymes non-covalently bound to a specific peptide backbone wherein said enzyme non-covalently bound to said peptide is capable of catalytic activity and wherein said scaffoldin is **obtained** from *Clostridium* sp. or wherein said peptide backbone comprises an amino acid sequence as shown in SEQ ID NO: 29. The specification further provides representative species of "dockerin" regions of enzymes **obtained** from *Clostridium* sp. but provides no teachings of derivatives thereof (see 112 second paragraph rejection). There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these compositions by any identifying structural characteristics or properties other than

the activities recited in the claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-7 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of enzymes non-covalently bound to a peptide backbone, using specific peptide backbones such as those **obtained** from *Clostridium* sp. comprising the amino acid sequence as shown in SEQ ID NO: 29 and specific dockerins, such as those obtained from *Clostridium* sp, does not reasonably provide enablement for any composition comprising any peptide backbone non-covalently bound to any enzyme, nor said composition wherein said enzyme is non-covalently bound to said peptide backbone by means of a "dockerin" derivative capable of non-covalently binding to said peptide backbone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7 and 11-13 are so broad as to encompass any composition comprising one or more enzymes non-covalently bound to any peptide backbone, wherein at least one of said enzymes is heterologous to said peptide backbone and said peptide

backbone is capable of having bound thereto a plurality of enzymes (claims 1-3, 6 and 7), wherein said peptide backbone comprises scaffoldin derived from a microorganism which produces a cellulosomal or amylosomal complex (claim 4, 5 and 11-13). Claims 14-16 are so broad as to encompass any compositions comprising any scaffoldin protein or any peptide backbone bound to any enzyme or any array of enzymes wherein said composition is produced recombinantly.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of compositions broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to teaching compositions of enzymes non-covalently bound to a peptide backbone, using specific

peptide backbones such as those **obtained** from *Clostridium* sp. comprising the amino acid sequence as shown in SEQ ID NO: 29 and specific dockerins, such as those obtained from *Clostridium* sp.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any peptide backbone or dockerin protein because the specification does **not** establish: (A) regions of the these proteins structure which may be modified without effecting non-covalently binding activity; (B) the general tolerance of these proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the binding activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction,

1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those peptide backbones of the claimed genus having the claimed binding activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any peptide backbone or dockerin protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those peptide backbones and dockerin derivatives having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Tokatlidis et al. (Protein Engineering Vol 6, No 8, pages 947-952, 1993, See IDS).

Tokatlidis et al. teach the properties conferred on *Clostridium thermocellum* endoglucanase CelC by grafting the duplicated segment of endoglucanase CelD. Specifically Tokatlidis et al. teach a composition comprising one or more enzymes bound to a peptide backbone, CipA, wherein said enzyme is heterologous to said peptide backbone and said backbone is capable of having bound thereto a plurality of enzymes.

Thus, Tokatlidis et al. anticipates claims 1-9 and 11-16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bayer et al. (See 892), Tokatlidis et al. (See IDS), and Gerngross et al. (See IDS).

Claims 1-9 and 11-16 are drawn to cellulosomes which contain at least one heterologous (See above 112 second paragraph rejection) enzyme.

Bayer et al. explicitly suggest "designer cellulosomes" in which a variety of different enzymes, from a variety of sources, may be incorporated into a cellulosome-like structure by several methods. Specifically, Bayer et al. teach:

> "exogenous enzyme types can be incorporated into the intact cellulosome using bifunctional crosslinking reagents. Alternatively, enzyme-dockerin chimeras can be combined either with a purified scaffoldin subunit, or with

> recombinant forms of scaffoldin that contain appropriate cohesins." (page 383, see Figure 4).
>
> "A more ambitious approach would be to substitute the resident cellulosomal components with heterologous enzymes that would be more suitable for a desired substrate. In this case, native scaffoldin could be used to integrate such enzymes into a complex, and the resultant 'heterocellulosome' would now exhibit the combined catalytic properties of the new group of enzymes.
>
> In order to incorporate heterologous enzymes into the complex, recombinant DNA (rDNA) technology can be used to fuse a given dockerin with a given enzyme in a surrogate bacterial strain. A desired scaffoldin can be produced separately, either from the native cellulosome, or by expressing the cloned protein in a different host. Assembly of the enzyme-dockerin chimeras onto the scaffoldin can then be performed in vitro, by virtue of the specific interactions with the intrinsic cohesins. In this manner, the set of enzymes in the cellulosome can be manipulated to suit the nature of the substrate. For example, hyperactive cellulases and xylanases from **different organisms**, or recombinant organisms can be bolstered with selected ligninases, pectinases, etc., which can be incorporated into the same enzyme complex in order to degrade a specific type of cellulose substrate efficiently." (page 384, column 1, paragraph 3, lines 1-4; column 2, lines 1-20).

In addition to suggesting heterocellulosomes and methods of constructing such complexes, Bayer et al. also suggest possible sources and types of enzymes available for use in heterocellulosome constructs. Bayer et al. (AB) teach that the enzymes may be selected "to suit the nature of the substrate," but specifically mention cellulases, xylanases, ligninases and pectinases. (see page 384, column 2, paragraph 2, lines 11-16). In relation to the source of the possible candidate enzymes, Bayer et al. teach:

> One of the exciting aspects of this approach is that thousands of cellulolytic strains have already been described. A growing list of strains are already suspected of expressing cellulosomes or related entities (see Box 1), all of which will be at the disposition of the prudent biotechnologist." (page 385, column 1, paragraph 3, lines 1-6; Box 1).

The examples of cellulolytic microorganisms, other than *Clostridium thermocellum*, that appear to produce cellulosome-like multienzyme complexes taught by Bayer et al. include *C. cellobioparum, C. cellulovorans, C. cellulolyticum C. josui, Bacillus circulans, Bacteroides cellulosolvens* and *Thermomonospora curvata*.

Although Bayer et al. explicitly suggest heterocellulosomes, methods of producing heterocellulosomes, specific enzymes and source organisms, Bayer et al. do not specifically teach a recombinantly produced cellulosome. Tokatlidis et al., however, teach a recombinantly produced *Clostridium thermocellum* endoglucanase, CelC, containing a dockerin domain isolated from a *Clostridium thermocellum* endoglucanase, CelD. "In contrast to CelC, CelC-CelD, was able to bind to CipA, a protein acting as a scaffolding component of the *Clostridium thermocellum* cellulase complex (cellulosome)." (page 947, abstract). The CipA scaffoldin protein of *Clostridium thermocellum*, discussed by Tokatlidis et al. (AN), is taught by Gerngross et al. (W) to be identical to the polypeptide backbone described by SEQ ID NO: 29 of the instant claims. Tokatlidis et al. also teach that "foreign proteins tagged with the duplicated segment (CelD dockerin domain) [can] be incorporated into the cellulosome in order to modify the enzymatic properties of the complex." (page 947, abstract). Thus, in light of the teachings of Bayer et al. and Tokatlidis et al. , it would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a cellulosome-like complex, as taught by Bayer et al. containing *Clostridium thermocellum* CipA as the scaffoldin and recombinantly produced enzymes comprising CelD dockerin domains, as taught by Tokatlidis et al. An artisan of ordinary skill in the

art would be motivated by the high likelihood of successfully producing a heterocellulosome by using the methods taught by Tokatlidis et al. and heteroenzymes suggested by Bayer et al. and by "the possibility of creating totally artificial multienzyme complexes ... [which] may have interesting properties to perform coupled enzyme reactions not necessarily related to cellulose degradation." (page 951, column 2, paragraph 2, lines 5-8).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
April 4, 2003